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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/035,708	03/05/98	ZEMLAN	F 1259-064

HM12/0124

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EXAMINER	
HAYES, R	
ART UNIT	**PAPER NUMBER**
1644	12

DATE MAILED: 01/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/035,708	Zemlan et al
Examiner	**Group Art Unit**
Robert C. Hayes	1645

☒ Responsive to communication(s) filed on *Nov 3, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-30* is/are pending in the application.

Of the above, claim(s) *1-13, 21, and 22* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *14-20 and 23-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-30* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 5 & 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644.

Election/Restriction

2. Applicant's election without traverse of Group VII, species-tau (claims 14-20 & 23-30, in Paper No. 11 is acknowledged.

Claims 1-13 & 21-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected inventions. Election was made **without** traverse in Paper No. 11.

Claim Rejections - 35 USC § 112

3. Claims 16-20, 25 & 27-29 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The human tau sequence from Goedert et al (1989) that is critical or essential to the practice of the invention, but not included in the claim(s), is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or

declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to Goedert et al (1989) is improper because Goedert is not a US patent, and because the tau sequence from Goedert et al (1989) is required in order to determine what constitutes a "sequence from serine199 to serine396 of tau protein". In addition, tau degradation products comprising ser199-ser396 of the human tau sequence disclosed in Goedert et al (1989) cannot be determined from that described within the instant specification without incorporation of Goedert's tau amino acid sequence into the specification; thereby, not being enabled until the specification is amended accordingly.

4. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The appropriate ATCC numbers and required Deposit information critical or essential to the practice of the invention, as it relates to monoclonal antibodies, cTau-7, cTau-8 and cTau-12, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the

enablement requirements of 35 USC §112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

The specification lacks any deposit information for the monoclonal antibodies, cTau-7, cTau-8 and cTau-12. Because these undefined monoclonal antibodies are unknown, and therefore, publicly not available or can reproducibly isolated from nature without undue experimentation, a suitable deposit for patent purposes is required. See M.P.E.P. 608.01(p)(C).

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification. In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Amendment of the specification to recite the date of deposit, the complete name and address of the depository, along with a *chain of custody,* are required.

5. Claims 14-20 & 23-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of assaying axonal damage of the CNS through identification of tau degradation products comprising ser199-ser396 of the human tau sequence disclosed in Goedert et al (1989) in the CSF, using deposited cTau-7, cTau-8 and cTau-12 Mabs, does not reasonably provide enablement for methods of determining axonal damage using structurally unknown and uncharacterized monoclonal antibodies, or for assaying unknown fragments of a structurally uncharacterized tau protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification describes a method of determining axonal damage in the human CNS though detection of 30 to 50 kDa degradation products of the human tau protein of Goedert et al (1989), which comprise ser199-ser396, using the specific monoclonal antibodies, cTau-7, cTau-8 and cTau-12. However, the name "monoclonal antibody" to a generic "axonally-derived protein", or even to a structurally uncharacterized "tau" protein itself, sets forth no structural characterization and little functional characteristics for determining when the skilled artisan is in possession of the required products for knowing how to make and use the instant invention. In contrast, the name "monoclonal antibody" encompasses any antibody directed to any biologically functional equivalent "axonally-derived protein", or fragment thereof; and the specification does not teach what amino acids are critical for detecting any axonally-derived protein that is indicative of axonal

damage in the CNS, except for possibly the epitopes recognized by cTau-7, cTau-8 and cTau-12 Mabs. In other words, structurally uncharacterized axonally-derived proteins encompass random modifications or mutations or truncations of different axonally-derived protein molecules, which would be expected by the skilled artisan to result in the generation of antibodies that cross-react with different proteins, or in the generation of antibodies that do not recognize the desired CSF human tau degradation products of the instant invention which, therefore, indicate axonal damage in the CNS. For example, Geysen et al. teach that random amino acid changes to a tetrameric peptide/epitope, which includes conservative substitutions to the same antigen, have "frequently been associated with loss of antibody binding" (e.g., pg. 38, 1st col., 2nd *pp*). Thus, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for any axonally-derived protein antibody binding reaction, except for that recognized by deposited cTau-7, cTau-8 and cTau-12 Mabs, would prevent the skilled artisan from determining whether any random proteolytic modification or truncation to the human tau protein of Goedert could be made that successfully results in the desired detection of axonal damage in the CNS for the instant invention, because any random mutation or modification or truncation manifested within a axonally-derived protein itself, would be predicted to adversely alter its biologically active 3-dimensional conformation, and therefore, the antigenic site itself; thereby, preventing the skilled artisan from knowing how to make and use the instant invention without undue experimentation to determine otherwise.

6. Claims 19-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, no reference sequence (i.e., tau SEQ ID NO) is recited in the claims for determining what constitutes a given position number for serine; thereby, making the claims ambiguous. It is suggested that amending claim 19 to recite specific amino acid positions corresponding to a specific human tau sequence (i.e., by SEQ ID NO, after appropriate submission of a Raw Sequence Listing) should obviate this particular rejection.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-20, 23-27, & 29-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Vandermeeren et al (WO 94/13795).

Vandermeeren et al. teach a method of determining CNS damage in the human CNS from patients with neurodegenerative diseases of the CNS including Alzheimer's disease (i.e., as it relates to claim 30), comprising use of monoclonal antibodies directed against the axonally-derived protein, tau, by treating cerebrospinal fluid with these monoclonal antibodies and

detecting antibody binding to tau by "conventional technology" (i.e., pg. 10) and gel electrophoresis/Western blotting in Fig. 4 (i.e., as it relates to claims 14, 16, 23 & 27), and by sandwich ELISA (i.e., pg. 11 & 15-16; as it relates to claim 26 & 29). In that comparison with CSF from control patients are disclosed on pages 19-29, the limitations of claim 15 are met. In that Figure 4 indicates multiple bands with apparent MWs from about 30 to 50 kDa, in which at least one tau protein fragment lacks native N-terminal or C-terminal amino acids (pg. 13; as it relates to claim 20), and comprises serine199 to serine 396 of tau (i.e., as it relates to claim 19), the limitations of claims 17-20 and 24-25 are met. It is noted that page 1 further discloses that tau "under normal circumstances promotes microtubule assembly and stability", and "is abundantly present in the axonal compartment of these neurons", and that CNS basal forebrain cholingeric neurons/axonal processes are well known to degenerate in Alzheimer's disease; thereby, anticipating the limitations of a method of determining axonal damage in the CNS through detection of tau in CSF, as currently claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RCH

Robert C. Hayes, Ph.D.
January 13, 2000

Christina Chan

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1600